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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,858	07/23/2001	Kazuo Kubo	049441-0127	1181

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OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

EXAMINER
BERCH, MARK L

ART UNIT	PAPER NUMBER
1624	14

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,858	KUBO ET AL.	
	Examin r	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48 and 51-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48 and 51-58* is/are rejected.

7)☒ Claim(s) *59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The restriction requirement is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

What role does "target" play in claim 52? What is the difference between an ordinary blood vessel and a "target blood vessel"? The traverse is unpersuasive. Page 30 just gives some examples, but one still does not know which are target blood vessels and which are not.

Claim 51 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other disorders, does not reasonably provide enablement for tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim sets forth the treatment of malignant cancer generally, except for leukemias, since nearly all cancers are tumors. However, there never has been a

compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The traverse is unpersuasive. It is understood that these are anti-angiogenesis compounds. Moreover, and more broadly, the skill level in this art is extremely low. Despite massive research with anti-angiogenesis agents, including antibody therapies, VEGF inhibitors, interferons, protease inhibitors, MMP inhibitors, protein fragments, RTK inhibitors, urokinase inhibitors, and integrin antagonists, as of the time of filing ---

and even as of the present moment --- not only have such efforts not produced a compound which treats cancer generally, such efforts have not produced any compounds which has been demonstrated efficacy for any cancer, period. That is, the history of anti-angiogenesis agents has, so far, been that of one disappointment after another.

Applicants point to their testing in example 4. Only one cell line was used, gliomas, so it could not demonstrate effectiveness generally. Moreover, the examiner must note that many compounds have TGIR figures so low (below 30%) that these would be considered as having failed the test.

Claims 1-48, 51-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the scores of examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." Hence, applicants must show that solvates can be made, or limit the claims accordingly.

The traverse is unpersuasive. Applicants state that "one of ordinary skill in the art can produce their solvates" --- but how? One of ordinary skill in the art knows that a given compound either forms a solvate or it does not. These compounds apparently do not, because they are not recovered as solvates. The fact that other quinazoline forms solvates is not relevant. Moreover, the actual compound showed was a quaternary salt, far more ionic than what is present here and hence more likely to forma a solvate. If these compounds do form solvates, how come no product was recovered as a solvate? This can be overcome by actually preparing a solvate, but since the working examples did not produce the solvate, it is not clear how this can be done. Applicants response should state specifically how to do it.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-48, 51-54, 56-57 are rejected under 35 U.S.C. 102(a) as being anticipated by JP 11-158149.

The reference has a publication date of June 15, 1999, prior to the 1/20/2000 date.

The traverse is unpersuasive. Applicants have supplied translations, but these are of no avail. The 11-253624 paper is dated later than the 6/15/99 date of the reference. The other three are all narrower than the claims. For example, 11-142493 and the other

two do not permit R1, R2 or R3 to be OH, alkoxy-carbonyl, carbamates and other choices.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 55 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-158149.

See above rejection. These claims call for Cl on the phenylene, while the species of the reference (see page 22) have F. However, the reference teaches halogen in general, so that the Cl would be an obvious variation as it is taught.

Claims 1-18, 47-52, 54, 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6,143,764.

The reference is the equivalent of WO 97/17329; the US equivalent is used for convenience; the PCT publication date of May 15, 1997 is relied on. It is also the same as EP 860433.

Note the following:

Example 153 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl)-N'-(2-methoxyphenyl)urea [113]

Example 154 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(3-methoxyphenyl)urea [114]

Example 155 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(4-methoxyphenyl)urea [99]

Example 156 N-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-N'-(2-fluorophenyl)urea [116]

Example 157 N-(4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl)-N'-n-butylurea [220]

These correspond to R^2 = R^3 = methoxy, R^{11} = substituted phenyl or butyl, all others = H. The same utilities are seen, note e.g. claim 44, 45. The sole difference is that applicants have a methyl group on the phenylene. Compounds that differ only by the

presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,* 138 USPQ 39. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph.

With regard to claims 3, and 15 (and thus all of 3, 8-13, 16-18, 47) these also have an extra methyl group on the urea nitrogen. Such a feature is taught in the definition of R5 at column 5, line 46, and is exemplified in compound 201 in column 35. Also, such a variation is considered obvious because of the close structural similarity. See *In re*

Hoeksema, 154 USPQ 169; *Ex parte Weston*, 121 USPQ 428; *Ex parte Bluestone*, 135 USPQ 199; *In re Doebel*, 174 USPQ 158.

Claim Objections

Claim 59 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Information Disclosure Statement

The AW reference was struck from one of the 1449 forms submitted. No database printout was supplied. Instead, applicants provided the underlying article itself, which has been cited.

Claim 59 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

December 24, 2002